

TEMPERATURE UNIFORMITY IN HYPERTHERMAL TUMOR THERAPY*

George H. Harrison, J. Eugene Robinson, and George M. Samaras
University of Maryland School of Medicine

SUMMARY

C3H mouse mammary tumors heated by water bath or by microwave-induced hyperthermia exhibit a response that varies sharply with treatment temperature; therefore, uniform heating of the tumor is essential to quantitate the biological response as a function of temperature. C3H tumors implanted on the mouse flank were easily heated to uniformities within 0.1°C by using water baths. Cold spots up to 1°C below the desired treatment temperature were observed in the same tumors implanted on the hind leg. These cold spots were attributed to cooling by major blood vessels near the tumor. In this case temperature uniformity was achieved by the deposition of 2450 MHz microwave energy into the tumor volume by using parallel-opposed applicators.

INTRODUCTION

Our group has carried out a series of hyperthermia studies by using third-generation transplants of spontaneous mammary tumors on the flanks of C3H mice. The tumors were heated by immersion in water baths and considerable effort was expended to characterize tumor thermal uniformity under treatment conditions (ref. 1). The results indicate that the tumors were uniform in temperature to within about 0.1°C and were within about 0.1°C of the core of the water bath.

Data taken with this tumor and water bath heating showed (fig. 1) a dramatic effect of hyperthermal treatment on tumor radiosensitivity (ref. 2). The increase in radiosensitivity was a strong function of treatment temperature. In addition, a comparison of these tumor data with comparable data from normal mouse skin showed that a therapeutic advantage might be gained by ionizing radiation treatment at elevated temperatures (ref. 2). Data from other laboratories, primarily from tumors implanted on the mouse leg and also heated by immersion in water baths (ref. 3), show smaller therapeutic advantages for similar water bath temperatures and X-ray doses. In addition, heat alone provides a therapeutic advantage, treatment sensitivity depending strongly on temperature.

HEATING METHODS

To broaden our heating capability we have developed microwave heating techniques applicable to small laboratory animals. (See refs. 4 and 5.)

*Supported in part by ACS Grant PDT-33 and USPHS NIH Grant CA 18872-01.

One of our approaches has been to surround the mouse tumor with solid or liquid bolus material in plane-parallel-slab geometry and to irradiate with parallel-opposed microwave beams, in direct analogy to conventional radiation therapy techniques used with ionizing radiation. Microwaves at 2450 MHz are delivered by simulated TEM waveguide applicators, time multiplexed so that tumor heating occurs from opposite sides (fig. 2). By using the semi-solid Guy-type muscle phantom material as bolus (ref. 6), tumor heating nonuniformities were at least 0.3°C .

One difficulty is that there are unavoidable temperature gradients from surface to interior in solid bolus material. In a stirred heated liquid bolus, these gradients would be negligible. The liquid also improves thermal coupling between bolus and tumor. Therefore, we are currently using a heated solution consisting of 80% (w/w) isotonic and saline and 20% (w/w) ethanol. Electric properties of this solution closely approximate those of wet tissues at 2450 MHz. Even when unstirred, substitution of the liquid bolus has resulted in substantially improved tumor heating uniformity and a significant reduction in thermal inertia. Faster liquid heat-up may be due to the realization of a more favorable bolus coupling geometry rather than to calorimetric properties of the solution, although the liquid phase promotes convective heat transfer between tissue and phantom. The bolus material is maintained at a temperature slightly lower than the desired tumor treatment temperature, and microwave energy supplies the additional required increment in heating.

TUMOR TEMPERATURE PROFILES

The parallel-opposed microwave heating apparatus has been used to treat tumors implanted on the flank and on the leg. Temperature distributions were measured by drawing small thermistor probes (YSI 514, 524) through the tumor, along parallel lines at different distances from the bone and leg muscle. As in the case of water bath heating, uniform temperature distributions were achieved for the flank tumors, that is, constant temperature to within $\pm 0.1^{\circ}\text{C}$, without the introduction of microwave power. In contrast, immersed leg tumors were quite nonuniform in temperature in the absence of microwave power. Figure 3 shows two thermal profiles taken through a leg tumor. The tumor was roughly ellipsoidal in shape and measured $15 \times 12 \times 8.5\text{ mm}$ along the three orthogonal major axes. The water bath in which it was immersed was maintained at 42.9°C . One profile was taken along a line near the leg bone, but well within the tumor. The second was taken about one-third of the way into the tumor on the side away from the bone. The profile shows marked temperature variations with temperatures measured as low as 41.6°C and 42.2°C for the thermal scans near and away from the bone.

Figure 4 gives another example of the cold central region near the bone of a smaller tumor ($10 \times 8 \times 5\text{ mm}$) also heated by immersion, together with the more uniform thermal pattern of tumors immersed in liquid bolus and microwave heated. The liquid bolus was maintained at 42.9°C and the tumor with bolus was irradiated with a microwave power of 22 watts. Heating with combined microwaves and temperature-controlled liquid bolus much improved the thermal uniformity as is shown in the two top curves.

DISCUSSION

Temperature nonuniformity of the tumors heated by water bath can be attributed to two factors: Major vessels run down both ventral and dorsal aspects of the leg and act as heat pipes to locally cool the tumor. In addition, in order to reach the inner aspect of the tumor, heat must be transferred through the muscle and bone of the leg. The cooling effect of blood flow near the bone is also evident in the lower temperature achieved near the bone when the tumor was microwave heated.

Because of the strong dependence of thermal and radiation sensitivities on temperature, the cold spots which we see in these tumors would markedly affect any measure of tumor response. In assays such as tumor cure and tumor regrowth time, the measured response is probably characteristic of the lowest treatment temperature experienced by any significant fraction of the tumor under treatment. Thus, these tumors on the leg immersed in water baths at 45.0° C might more appropriately be compared with uniformly heated tumors immersed in water baths 1° to 1.5° C lower in temperature.

These observations might have some bearing on the discrepancies in biological hyperthermia data on different tumors subjected to apparently similar thermal treatments. They should stand as a reminder that careful thermal studies are even more important to thermobiology than good radiation dosimetry is to conventional radiobiology.

REFERENCES

1. Robinson, J. E.; McCulloch, D.; and Edelsack, E. A.: Evaluation of Tumor Immersion Technique for Radiobiological Hyperthermia Studies. *Med. Phys.*, vol. 2, 1975, p. 159 (abstract).
2. Robinson, J. E.; Wizenberg, M. J.; and McCready, W. A.: Hyperthermia and Radiation - Response of Normal Tissue In Situ. *Radiology*, vol. 13, 1974, pp. 195-198.
3. Thrall, D. E.; Gillette, E. L.; and Dewey, W. C.: Effect of Heat and Ionizing Radiation on Normal and Neoplastic Tissues of the C3H Mouse. *Radiat. Res.*, vol. 63, 1975, pp. 363-377.
4. Robinson, J. E.; McCulloch, D.; and Edelsack, E. A.: Microwave Heating of Malignant Mouse Tumors and Tissue Equivalent Phantom Systems. *J. Microwave Power*, vol. 11, 1976, pp. 87-98.
5. Cheung, A. Y.; Dao, T.; and Robinson, J. E.: Dual Beam TEM Applicator for Direct Contact Heating of Dielectrically Encapsulated Malignant Mouse Tumor. *Radio Science*, vol. 5, no. 65, 1977, pp. 81-85.
6. Guy, A. W.: Analyses of Electromagnetic Fields Induced in Biological Tissues by Thermographic Studies on Equivalent Phantom Models. *IEEE Trans. Microwave Theory Tech.*, MTT-19, no. 2, 1971, pp. 205-214.

EFFECT OF HYPERTHERMIA ON TUMOR CURE

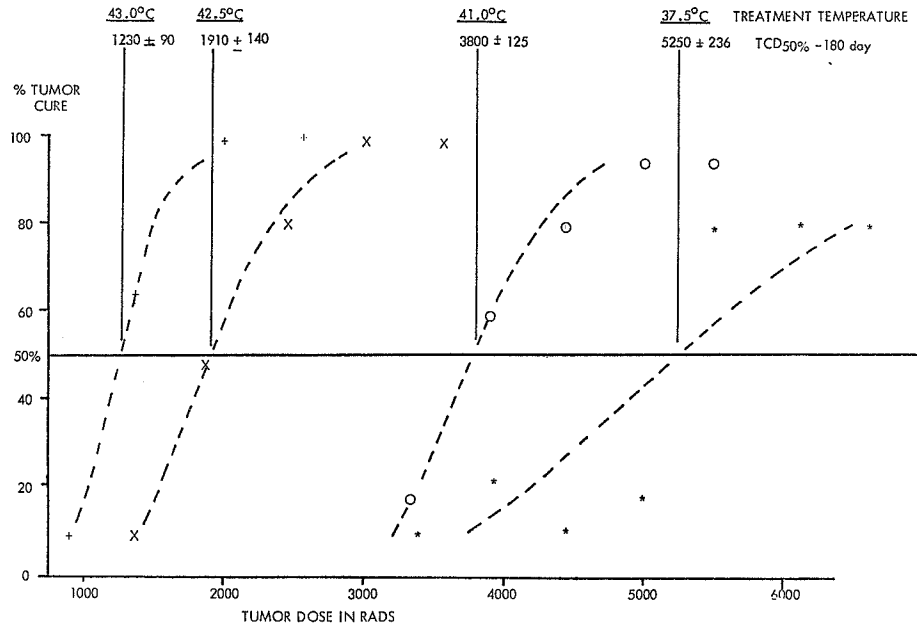
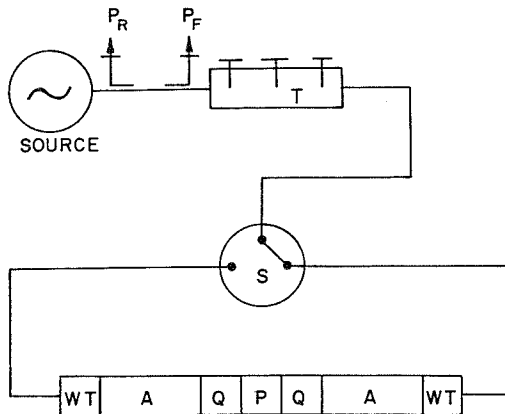


Figure 1.



P = FORWARD POWER
 P = REFLECTED POWER
 P = TISSUE EQUIVALENT MATERIAL + TUMOR
 Q = QUARTER WAVE TRANSFORMER
 A = APPLICATOR
 WT= WAVEGUIDE TUNER
 S = SWITCHING DEVICE
 T = COAXIAL TUNER

Figure 2.

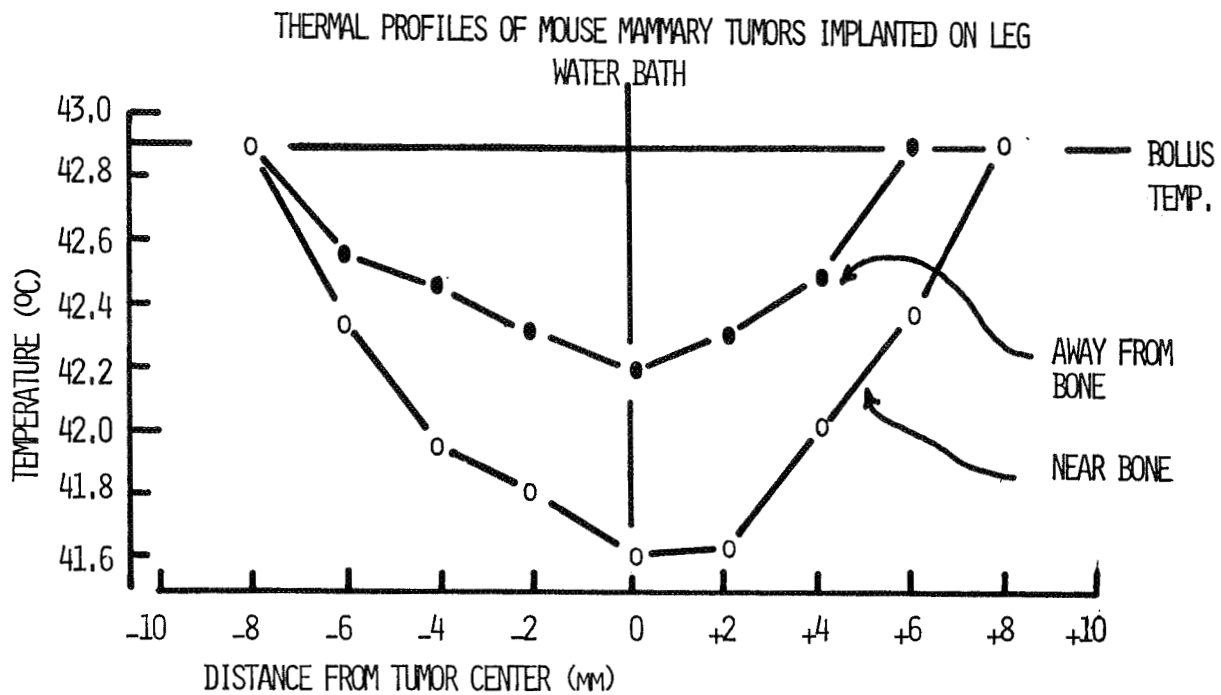


Figure 3.

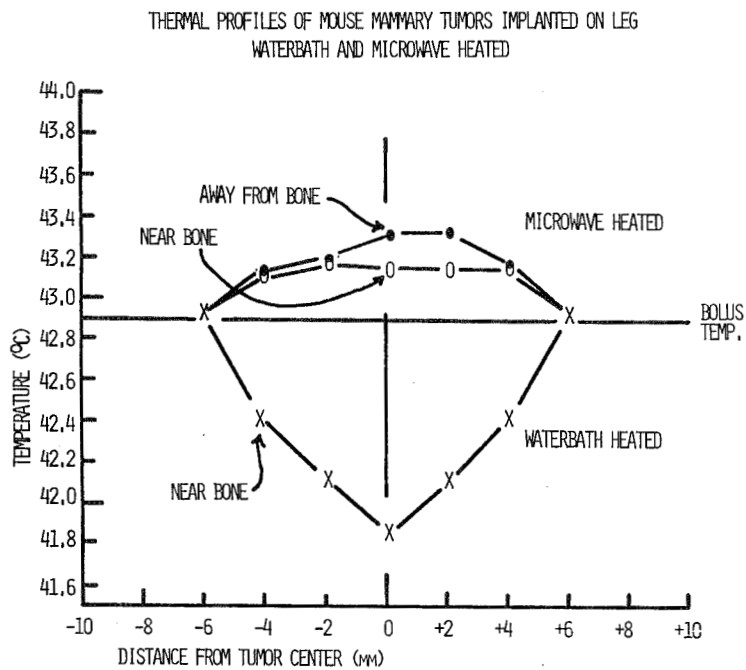


Figure 4.

Questions and Answers Following Harrison's Paper

Singh: Were these temperature measurements simultaneous with the heating?

Harrison: These were all from cooling curve measurements. We had very poorly characterized E&M fields, and we were using metallic hypodermic thermistor probes with thermistors. In fact, we did not dare attempt to make measurements with the microwaves on, so each and every datum point you see is an extrapolated temperature point from a cooling curve.

Carr: When you showed the apparatus on one of your slides, you showed that you were using two microwave sources simultaneously?

Harrison: No, not simultaneously. They switch back and forth. We have a timing circuit. We switch back and forth about every few seconds or so.

Baker: What was the composition of your solid, or semi-solid, bolus that you used?

Harrison: I cannot remember. It is the one that Guy uses that has polyethylene, powder, and water, or saline, I guess.